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Diagnosis and outcome of oesophageal Crohn's disease

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Abstract: BACKGROUND AND AIMS Crohn's disease (CD) can involve any part of the gastrointestinal tract. We aimed to characterize clinical, endoscopic, histologic features and treatment outcomes of CD patients with oesophageal involvement. METHODS We collected cases through a retrospective multicentre European Crohn's and Colitis Organisation CONFER [COllaborative Network For Exceptionally Rare case reports] project. Clinical data were recorded in a standardized case report form. RESULTS A total of 40 patients were reported [22 males, mean (±SD, range) age at oesophageal CD diagnosis: 25 (±13.3, 10-71) years and mean time of follow-up: 67 (±68.1, 3-240) months]. Oesophageal involvement was established at CD diagnosis in 26 patients (65%) and during follow-up in 14. CD was exclusively located in the oesophagus in 2 patients. Thirteen patients (32.2%) were asymptomatic at oesophageal disease diagnosis. Oesophageal strictures were present in 5 patients and fistulizing oesophageal disease in one. Eight patients exhibited granulomas on biopsies. Proton-pump inhibitors (PPIs) were administered in 37 patients (92.5%). Three patients underwent endoscopic dilation for symptomatic strictures and none oesophageal-related surgery. Diagnosis in pre-established CD resulted in treatment modifications in 9/14 patients. Clinical remission of oesophageal disease was seen in 33/40 patients (82.5%) after a mean time of 7 (±5.6, 1-18) months. Follow-up endoscopy was performed in 29/40 patients and 26/29 (89.7%) achieved mucosal healing. CONCLUSION In this case series the endoscopic and histologic characteristics of isolated oesophageal CD were similar to those reported in other sites of involvement. Treatment was primarily conservative, with PPIs administered in the majority of patients and modifications in pre-existing IBD-related therapy occurring in two thirds of them. Clinical and endoscopic remission was achieved in more than 80% of the patients.

DOI: https://doi.org/10.1093/ecco-jcc/jjz201

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-181115
Journal Article
Accepted Version

Originally published at:
Vale Rodrigues, Rita; Sladek, Margaret; Katsanos, Konstantinos; van der Woude, C Janneke; Wei, Juan; Vavricka, Stephan R; Teich, Niels; Ellul, Pierre; Savarino, Edoardo; Chaparro, Maria; Beaton, David; Oliveira, Ana Maria; Fragaki, Maria; Shitrit, Ariella Bar-Gil; Ramos, Laura; Karmiris, Konstantinos (2020). Diagnosis and outcome of oesophageal Crohn's disease. Journal of Crohn's Colitis, 14(5):624-629.
DOI: https://doi.org/10.1093/ecco-jcc/jjz201

Diagnosis and outcome of esophageal Crohn's disease

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Short title: Esophageal Crohn's disease

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Abstract:

Background and aims: Crohn's disease (CD) can involve any part of the gastrointestinal tract. We aimed to characterize clinical, endoscopic, histologic features and treatment outcomes of CD patients with esophageal involvement.

Methods: We collected cases through a retrospective multicentre European Crohn's and Colitis Organisation CONFER [COllaborative Network For Exceptionally Rare case reports] project. Clinical data were recorded in a standardized case report form.

Results: A total of 40 patients were reported [22 males, mean (±SD, range) age at esophageal CD diagnosis: 25 (±13.3, 10-71) years and mean time of follow-up: 67 (±68.1, 3-240) months]. Esophageal involvement was established at CD diagnosis in 26 patients (65%) and during follow-up in 14. CD was exclusively located in the esophagus in 2 patients. Thirteen patients (32.2%) were asymptomatic at esophageal disease diagnosis. Esophageal strictures were present in 5 patients and fistulizing esophageal disease in one. Eight patients exhibited granulomas on biopsies. Proton-pump inhibitors (PPIs) were administered in 37 patients (92.5%). Three patients underwent endoscopic dilation for symptomatic strictures and none esophageal-related surgery. Diagnosis in pre-established CD resulted in treatment modifications in 9/14 patients. Clinical remission of esophageal disease was seen in 33/40 patients (82.5%) after a mean time of 7 (±5.6, 1-18) months. Follow-up endoscopy was performed in 29/40 patients and 26/29 (89.7%) achieved mucosal healing.

Conclusion: In this case series the endoscopic and histologic characteristics of isolated esophageal CD were similar to those reported in other sites of involvement. Treatment was primarily conservative, with PPIs administered in the majority of patients and modifications in pre-existing IBD-related therapy occurring in two thirds of them. Clinical and endoscopic remission was achieved in more than 80% of the patients principally with conservative management.

Keywords: Crohn's disease, Esophagus

Introduction

Crohn's disease (CD) is a lifelong disease arising from an interaction between genetic and environmental factors. It can involve any part of the gastrointestinal tract, but the most common locations are the terminal ileum and colon. Esophageal involvement is not usual. Nevertheless, more than 100 cases of esophageal CD have been published since the first report of Franklin and Taylor in 1950[1-3]. Prevalence of 0.3-10% is suggested in adults but population-based studies are lacking[3-7]. More frequent esophageal involvement has been implicated in studies reporting on pediatric CD patients (4.2-42%)[8,9]. Wide variations are generally attributed to whether asymptomatic patients with histological involvement are included in the analysis. Gastroduodenoscopy is not considered a pre-requisite for CD mapping in most guidelines and especially in asymptomatic adults[9,10].

Esophageal CD can present as an erosive–ulcerative esophagitis, esophageal stricture, or fistula, thus sharing many features of other more common diseases of the esophagus (reflux esophagitis, infection, drug-induced, related to malignancy or autoimmune diseases). The histologic features of esophageal CD may be nonspecific further adding on diagnostic challenge. The optimal treatment of esophageal CD is unknown because controlled trials are lacking. Most physicians use proton pump inhibitors (PPI) as an add-on regimen to conventional therapy and have a lower threshold for starting anti-TNF therapy compared to disease located elsewhere, given the expected poor prognosis[10].

We aimed to describe diagnostic work-up, interventions and outcome of a series of patients with CD located in the esophagus.

Materials and Methods

Study design

This was a European Crohn's and Colitis Organization (ECCO) retrospective observational multicentric study performed as part of CONFER [COllaborative Network For Exceptionally Rare case reports] project. The CONFER project is an ECCO initiative aiming to identify, assemble and report together rare Inflammatory Bowel Disease (IBD) cases of clinical relevance, which are otherwise seldom reported. The core of CONFER methodology is selecting certain topics worthy of investigation out of case proposals submitted by ECCO members. The Steering Committee makes an initial selection, identifying those cases with the highest scientific interest and proximity to the purpose of CONFER project. A Feasibility Network, comprised of 30-35 high volume IBD centers around the globe, is asked to identify similar cases and the final decision is again taken by the Steering Committee based on the outcome of networking. This topic then becomes a CONFER project. ECCO launches a call to identify similar cases encountered by IBD physicians worldwide using several tools; announcements in the ECCO annual congress and in national and international IBD meetings across Europe, e-mailing to all ECCO members, posting in ECCO website and ECCO eNews, flyers and personal communication between ECCO members. Physicians are then prompted to report their case(s) using a pre-determined standardized case report form. The call for the present case series was entitled "*Esophageal Crohn's Disease"*.

Patients and procedures

All CD patients with esophageal involvement diagnosed either throughout the course of CD or at diagnosis were eligible for inclusion in this study. Diagnosis of esophageal CD was based on clinical presentation, endoscopic appearance and histological findings[10]. Esophageal involvement was histologically proven in all patients reported in this case series. Data were collected using a case report form, which was divided into two main sections. Section 1 included patient (epidemiological data, past medical history, alcohol consumption/smoking, family history) and disease (date of diagnosis, Montreal classification, extraintestinal manifestations and treatment)

characteristics. Section 2 included a description of esophageal CD: disease location, endoscopic and histological findings, treatment of CD at esophageal diagnosis, interventions, treatment modifications and course of disease. Relevant laboratory and radiologic tests were also recorded. Data were collected and analyzed anonymously and handled according to local regulations. Informed consent was obtained, where obligatory.

Statistics

All statistical analyses (frequencies, descriptive statistics) were done with SPSS 20.0 software package (IBM SPSS Statistics, Armonk, NY, USA).

Results

Patients' background information

A total of 15 centers responded to our call and 50 cases were initially reported. Ten patients were excluded due to lack of compatible histologic data and thus 40 cases were included in the analysis. Patients' characteristics are shown in Table 1. Mean (±SD, range) age at CD diagnosis was 23 years (±12.6, 3-71). Only 2 patients (5%) were current smokers. A family history of IBD was reported in 7.5% of patients. CD was exclusively located in the upper GI tract in 4 patients and solely in the esophagus in 2 while in the rest, ileal disease was present in 9 (22.5%), colonic in 3 (7.5%) and ileo-colic in 24 (60%) patients. Gastric involvement was generally seen in 15 patients (37.5%). Of those, only two had active *Helicobacter pylori* infection. Thirteen patients (32.5%) had received at least one anti-tumor necrosis factor (TNF) agent and six (15%) had undergone a CD-related surgery (partial small bowel resection, stricturoplasty, partial colectomy, ileocecal resection or rectal abscess drainage) prior to esophageal involvement diagnosis.

Esophageal CD diagnosis

Esophageal disease characteristics are summarized in Table 2. Mean IBD duration until esophageal disease diagnosis was 2.9 (±5.7, 0.0–27.9) years, with a mean age at diagnosis of 25 (±13.3, 10-71) years. Esophageal involvement was established at CD diagnosis in 26 patients (65%) and during follow-up in 14 (35%). Most patients had at least one additional test to exclude more common diagnoses (n=35, 87.5%); contrast esophageal examination in 12 patients (30%), Interferon Gamma Release Assay (IGRA) in 27 (67.5%), tuberculine skin test in 18 (45%), esophageal brushing for *Candida spp* in 11 (27.5%), an angiotensin converting enzyme test in 5 (12.5%), antibodies against human immunodeficiency virus (HIV) in 29 (72.5%), mycological infection staining on biopsy in 19 (47.5%), *Ziehl–Nielsen* stain in 11 (27.5%), polimerase chain reaction for *Mycobacterium tuberculosis* in 4 (10%), chest CT in 12 (30%), chest X-ray in 28 (70%), esophageal manometry in 5 (12.5%) or 24-hour esophageal pH test in 5 (12.5%). Laboratory testing was abnormal in most of the patients at esophageal disease diagnosis, with elevated C-reactive protein in 23 patients [mean 2.9 (±1.9, 1.0-7.0) mg/dL] and elevated

erythrocyte sedimentation rate in 24 [mean 44 (±18.4, 26.0-94.0) mm/h]. Sixteen patients (40%) had anemia [mean hemoglobin value 9.8 (±2.3, 6.0-12.0) g/dL].

The most common symptom was dysphagia or odynophagia in 19 patients (47.5%). Thirteen patients (32.5%) were asymptomatic at esophageal disease diagnosis. Distal esophagus was the most common site of involvement, either alone (n=15, 37.5%) or as part of involvement of the entire esophagus (n=10, 25%). There were several endoscopic findings, but erosions and small ulcers were more frequently seen (n=31, 77.5%). Interestingly, one patient presented with an esophageal fistula. Representative pictures of endoscopic findings are shown in Figure 1.

On histology, seventeen patients (42.5%) had acute and chronic inflammation while 12 (30%) were found to have chronic inflammation with predominantly lymphocytes and plasma cells. Non-caseating granulomas were less frequently seen (20%).

Esophageal disease treatment and outcomes

Thirty-four patients (85%) had an inflammatory phenotype of esophageal CD and were treated with a variety of medications (Table 2). Proton-pump inhibitors (PPIs, n=37, 92.5%) were administered in the majority of patients. Three patients underwent endoscopic dilation for symptomatic strictures and none CD-related esophageal surgery. CD was active either clinically and/or endoscopically in the majority of patients at esophageal involvement diagnosis (>80%). Interestingly, esophageal disease diagnosed during CD follow-up (14/40) resulted in treatment modifications in 9/14 patients, excluding PPIs use, 6 of them also with extra-esophageal clinical activity: 5 started systemic corticosteroids, 2 topical steroids (fluticasone), one anti-TNF and one methotrexate. Thirty-three patients (82.5%) were successfully treated with complete resolution of symptoms after a mean time of 7 (±5.6, 1.0-18.0) months. Follow-up endoscopy was performed in 29 patients and 89.7% achieved mucosal healing. Of the 2 patients with isolated esophageal disease, one was treated only with PPI with complete symptomatic resolution while the other required combined endoscopic and medical therapy initially with PPI and systemic corticosteroids and subsequently administration of thiopurine and anti-TNF; both had achieved mucosal healing at last follow-up.

Discussion

This is a retrospective, international study reporting a series of CD patients with esophageal involvement. Although this study was not designed to assess the prevalence of esophageal CD, we can infer that onset of this presentation may be under-recognized due to the infrequent performance of upper GI endoscopy in asymptomatic individuals with CD, especially adults.

Diagnostic work up includes a combination of esophageal-specific symptoms, a history of extra-esophageal CD, and endoscopic and histologic features that are supportive but not specific for CD. Almost one third of the patients in our series were asymptomatic while the rest complained of non-specific symptoms like dysphagia/odynophagia, heartburn, vomiting, chest pain and weight loss, resembling gastro-esophageal reflux disease, similar to previous reports.[3, 5, 7] Most patients had at least one additional test to exclude more common diagnoses (87.5%). CD of the esophagus is not difficult to diagnose in cases in which other segments of the digestive tract are simultaneously involved or in patients with a prior history of CD, but isolated esophageal disease requires exclusion of more common esophageal diseases, so we suggest that in the absence of a previous diagnosis of CD, an exclusion of GERD (based on pH impedance study), infectious esophagitis (based on specific stains at least for Candida and Cytomegalovirus) and granulomatous diseases such as tuberculosis and sarcoidosis (based on imaging and laboratory tests) should be made.

Endoscopic features are not pathognomonic. Wang *et al.* proposed that esophageal CD progresses through three phases. The initial phase involves inflammation, edema, erosions and linear ulcers without significant symptoms, then there is a progression to stenotic lesions with mucosal bridges and finally patients present with progressive dysphagia, odynophagia, vomiting and weight loss and severe complications on the ground of fibrotic strictures and fistulae.[11] Distal superficial ulcers, erosions and/or erythema were common in our cohort as described in other reports.[3, 5, 7] However, stenotic lesions necessitating interventions were uncommon and only one patient had developed a fistula.

Histological features are also not always compatible with CD. In our cohort, chronic inflammation was the most common presentation; eight patients (20%) had non-caseating granulomas in the

setting of chronic inflammation, a higher rate than the one reported in the literature (7-9%), perhaps due to the inclusion of pediatric patients as granuloma formation is more often seen in younger patients, and mainly in the severe, active penetrating disease.[12,13]

CD limited to the esophagus is rare and has been described in case reports.[6,11,14,15] In our cohort there were only 2 cases. Esophageal involvement was established at CD diagnosis in two thirds of the patients (65%) and during follow-up in one third (35%). Almost half of the patients demonstrated perianal disease, which is also in line with previous reports.[16] One third of the cohort had extra-intestinal manifestations, slightly less than global data for CD, which can also be justified by the inclusion of pediatric patients.[17]

There are limited data on the most suitable management of esophageal CD due its rarity and the frequent coexistence of distal disease which leads to the use of standardized therapeutic protocols. ECCO guidelines suggest treating mild esophageal CD with PPI only and more severe or refractory disease with systemic corticosteroids or an anti-TNF-based strategy.[10] De Felice *et al* suggested treating esophageal CD based on disease behavior.[3] This cohort confirms this strategy with the vast majority of patients being treated with a PPI and less patients with more complicated or persistently active disease at esophageal involvement diagnosis requiring step-up therapies. Esophageal disease diagnosed during follow-up resulted in medical treatment modifications in 64.3% of patients, two thirds of whom (66.7%) had also extra-esophageal clinical activity.

The limitation of the CONFER methodology should be acknowledged, as it relies on voluntary submission of cases by physicians responding to ECCO calls, which could introduce geographical and other selection biases. However, we believe this caveat is offset by the benefits of this methodology for identifying and reporting larger case series of rare events, which are otherwise seldom reported in a single case-report format. The sample size is relatively small and thus no risk factors or predictors can be investigated. Follow-up endoscopy was not available in all patients.

In conclusion, esophageal involvement can be detected either at CD diagnosis or during follow-up, manifesting as the only site of CD location in rare cases. Characteristics are similar to those of other sites of involvement and diagnosis can be challenging and performed even during CD

being in remission. Optimal treatment is conservative but not consensual depending also on extra-esophageal sites of involvement, with PPIs administered in the majority of patients and treatment modifications occurring frequently, when diagnosed at a later phase. Properly designed, ideally prospective studies are needed to identify more reliable diagnostic criteria and phenotypes of esophageal CD that predict response to specific medical therapies. However, until further data are available, this needs to be a case-by-case decision.

Acknowledgements

The authors would like to thank the ECCO CONFER Steering Committee members: Uri Kopylov (Israel), Gionata Fiorino (Italy), Shaji Sebastian (United Kingdom) and Pierre Ellul (Malta) and the ECCO Clinical Committee members: Marc Ferrante (Belgium), Javier Gisbert (Spain), Kristina Gecse (Hungary), John Mansfield (Great Britain), Laurent Beaugerie (France) and Peter Bossuyt (Belgium) and all collaborators participating in the Feasibility Network for selecting this topic as a CONFER project and providing their insightful comments as well as the ECCO Office personnel for their valuable contribution to the success of the project.

Potential conflicts of interest: No financial support was received for this work.

Specific author contributions

Rita Vale Rodrigues and Konstantinos Karmiris conceived the study, analyzed and interpreted the data and drafted the manuscript; Margaret Sladek, Konstantinos Katsanos, C. Janneke van der Woude, Juan Wei, Stephan Vavricka, Niels Teich, Pierre Ellul, Edoardo Savarino, Maria Chaparro, David Beaton, Ana Maria Oliveira, Maria Fragaki, Ariella Bar-Gil Shitrit and Laura Ramos contributed the cases and critically revised the manuscript.

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Figure legend

Figure 1: Endoscopic findings: A- focal erythematous spots, B- erosions, C and D- deep ulcerations, E and F- stenosis and pseudopolyps

Table 1. Patient demographics and Crohn's disease characteristics

Characteristic	Patients (n=40)
Mean (±SD, range) age at diagnosis (years)	23 (±12.6, 3-71)
Gender	
Male	22 (55%)
Female	18 (45%)
Race	
Asian/Oriental	6 (15%)
Caucasian/White	34 (85%)
Ethnicity	
Hispanic or latino	5 (12.5%)
Non-Hispanic or non-latino	35 (87.5%)
Geographical spread	
Poland	8 (20%)
China	3 (7.5%)
The Netherlands	4 (10%)
Portugal	3 (7.5%)
Spain	2 (5%)
Greece	6 (15%)
Switzerland	4 (10%)
Germany	3 (7.5%)
Italy	2 (5%)
Malta	2 (5%)
United Kingdom	2 (5%)
Israel	1 (2.5%)
Positive family history of IBD	3 (7.5%)
Smoking	

Current	2 (5%)
Former	2 (5%)
Non-smoker	36 (90%)
Montreal Classification – age	
<=16	18 (45%)
17-40	20 (50%)
>40	2 (5%)
Montreal Classification – location	
L1	9 (22.5%)
L2	3 (7.5%)
L3	24 (60%)
Isolated L4	4 (10%)
Montreal Classification – behavior	
B1	22 (55%)
B2	8 (20%)
B3	10 (25%)
Perianal disease	18 (45%)
Extra-intestinal manifestations	14 (35%)
Ocular – uveitis / episcleritis	1 / 1
Osteoarticular – peripheral arthropathy	5
Skin – erythema nodosum	6
Oral granulomatosis	3
Prior IBD treatment	
5-aminosalicylic acid	14 (35%)
Systemic corticosteroids	12 (30%)
Anti-TNF	13 (32.5%)
Thiopurines	16 (40%)

Methotrexate	3 (7.5%)
Surgery	6 (15%)

Table 2. Characteristics of esophageal CD

Characteristic	Value (n=40)
Age (±SD, range) at diagnosis (years)	25 (13.3, 10-71)
Course of disease	
Esophageal disease at diagnosis	26 (65%)
Esophageal disease at follow-up	14 (35%)
Symptoms	
Dysphagia/Odynophagia	19 (47.5%)
Heartburn	8 (20%)
Vomiting	3 (7.5%)
Chest pain	8 (20%)
Weight loss	8 (20%)
Asymptomatic – Incidental finding at endoscopy	13 (32.5%)
Location	
Proximal	6 (15%)
Mid	9 (22.5%)
Distal	15 (37.5%)
Entire esophagus	10 (25%)
Endoscopic findings	
Erosions or small ulcers	31 (77.5%)
Deep ulceration	7 (17.5%)
Patchy erythema	6 (15%)
Multiple focal erythematous spots	6 (15%)
Stricture	5 (12.5%)
Fistula	1 (2.5%)
Esophageal histology	
Presence of granulomas	8 (20%)

Acute and chronic inflammation	17 (42.5%)
Chronic inflammation	12 (30%)
Acute inflammation	2 (5%)
IBD disease activity at esophageal CD diagnosis	
Clinically active	33 (84.6%)
Endoscopically activity	35 (89.7%)
CT or MR enterography evidence of disease	21 (53.8%)
Treatment after diagnosing of esophageal CD	
Proton Pump Inhibitor	37 (92.5%)
5-aminosalicylic acid	16 (40%)
Systemic corticosteroids	21 (52.5%)
Anti-TNF	23 (57.5%)
Thiopurines	19 (47.5%)
Enteral nutrition	6 (15%)
Endoscopic dilation	3 (7.5%)

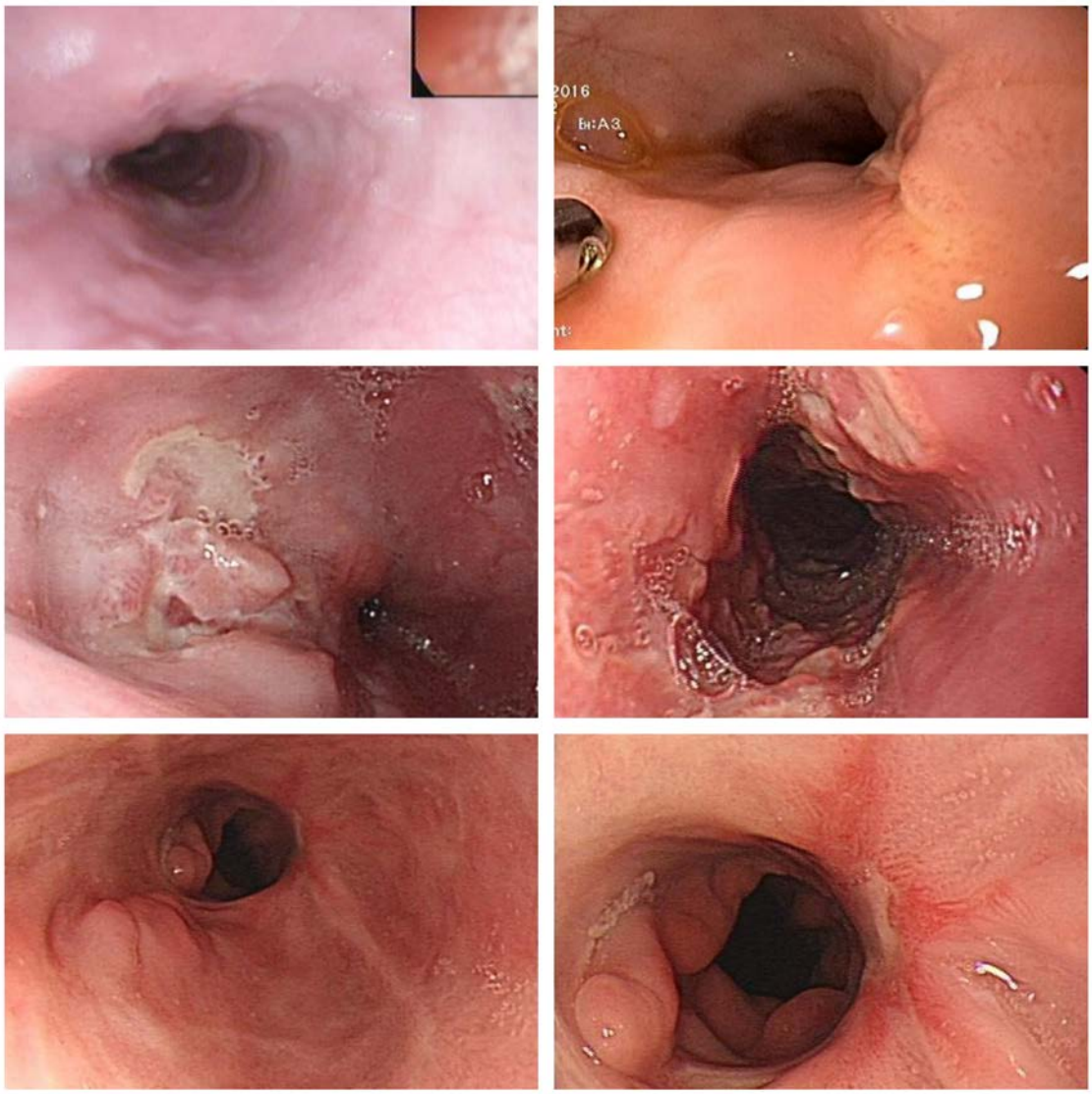

Figure 1. Endoscopic findings: A- focal erythematous spots, B- erosions, C and D- deep ulcerations, E and F- stenosis and pseudopolyps